REMARKS

I. On page 2 of the Office Action, the Examiner asserted two (2) objections: 1) the Sequence Listing apparently does not list all of the sequences disclosed in the application; and 2) claims 4 and 7 are multiply dependent.

The Examiner indicated that sequences on page 40 are not in the Listing.

The 15 primers of page 40 are now denoted with identifiers. Also, a sequence was identified on page 39. That sequence contained an evident and obvious typographic error and now is denoted with an identifier.

Claim 4 was made dependent on claim 3 and new claims analogous to claim 4 but dependent on claims 1 and 2 were introduced. A similar approach was taken with respect to claim 17.

Hence, the objections can be removed.

II. On pages 2 and 3 of the Office Action, the Restriction Requirement was made final. Also, the Examiner requested that claim 1 be rephrased in terms of SEQ ID NO:2 and SEQ ID NO:4.

The non-elected claims have been canceled, and the request of the Examiner was adopted.

III. On pages 3 and 4 of the Office Action, claim 1 was rejected as allegedly

being non-statutory (i.e., does not fall into one of the statutory classes of patents: e.g., an article of manufacture, machine, composition of matter or process). The Examiner suggested that the rejection can be overcome most readily by amending the claim to include "isolated" or "purified" to modify the word "antibody" in the preamble.

Claim 1 was so modified and thus the rejection can be removed.

IV. On pages 4 and 5 of the Office Action, claims 1-4 and 17 were rejected as allegedly being indefinite. The issues focus on: 1) lack of adequate information regarding CDRs; 2) the meaning of conformational epitopes; 3) use of a specific phase (i.e., "capable of"); 4) appropriateness of polyclonal antibody within the generic scope of the independent claim; and 5) requirement of positive process steps in a method claim.

The issues will be discussed and traversed seriatim.

a. Information Regarding CDRs

Briefly, the Examiner asserted that to generate a functional molecule by antibody grafting, one of skill in the art must know both framework regions and all of the CDRs comprising the molecule.

A review of the patent literature for humanized antibodies does not support that position. So long as one CDR is defined, nothing more is required as an artisan would know how to use that one CDR and to provide the remainder of the sequences to yield a functional molecule. Framework regions are known in the art and one need not describe what is readily know in the art (moreover, the frameworks are described in the

specification).

Attached hereto are copies of Laune et al., Journal of Biological Chemistry, 272:30937-30944, 1997, and Feng et al., Journal of Biological Chemistry, 273:5625-5630, 1998, both of which teach that a single CDR is sufficient for obtaining specific binding.

b. Conformational Epitopes

Issued US patents use "conformational epitopes" as a claim element. A search of the USPTO website for "conformational epitopes" resulted in 7 hits, see, for example, US Pat. No. 5,618,536. The term is used in the issued patent (art recognized term), and thus, one of skill in the art would know the metes and bounds of the term.

Also, an artisan can readily determine a conformational epitope, for example, using an ELISA and natural and denatured antigen. Thus, the term is not indefinite.

c. Capable Of

Similarly, "capable of" is recited as a claim element in 173,221 issued US patents. Thus, the term is commonly used in issued patents (art recognized term), and one of skill in the art would know the metes and bounds of the term.

However, an alternative has been substituted in the claim.

d. Polyclonal Antibody

There is no doubt that a particular antibody of interest having SEQ ID NO:2 or 4 can be found in a polyclonal antiserum. To provide further clarity, claim 2 was revised

to include "one of a polyclonal antiserum."

e. Positive Process Step

Regarding the assertion of alleged missing steps, claim 17 was modified to include positive process steps.

Thus, the issues having been addressed, the rejection can be removed.

V. On pages 5-7 of the Office Action, claims 1-4 and 17 were rejected for allegedly being non-enabled. Specifically the Examiner intimated that the scope of the claims is too broad.

The rejection is traversed for the following reasons.

In a brief telephonic interview with the Examiner, it appeared the Examiner viewed the sequence as separate from the CDRs (e.g., the sequence recited can exist anywhere on the antibody). Put another way, the Examiner may believe an antibody may have the sequence, but the sequence does not provide the mechanism for recognition.

The rejection is traversed for the following reasons.

Claim 1 was revised to tie the specific sequences recited to particular CDRs. Such a construction directs the sequences to the CDRs and not to other parts of the antibody molecule. Concomitantly, that change to the claims serves to define more clearly the CDR regions (i.e., by sequence).

Moreover, as attested by the attached two references, clearly providing at least

one CDR is sufficient to practice the instant invention.

Regarding the issue of claim 2 raised in the third full paragraph on page 7, claim 2 depends on claim 1, the change to claim 1 above structures the claim to those antibodies having SEQ ID NO:2 or 4 at those particular sites, whatever the source of the antibody.

Hence, the Examiner has not made out a prima facie case of non-enablement. Accordingly, the rejection can be removed.

VI. Beginning at page 8 of the Office Action, claims 2, 4 and 17 were rejected as allegedly being anticipated by the disclosure of any of multiple cited references.

Each rejection is discussed and traversed separately.

a) Claims 2 and 4 were rejected under 35 U.S.C. 102(a) over Nakano et al.

Nakano et al. relate to linear epitopes. For example, on page 7101, right column, towards the bottom of the page, Nakano et al. review the state of the art and note that antibodies directed to E2 contain several linear epitopes.

As to the particular antibodies raised in the experimentation described by Nakano et al., the authors believed antibodies are directed to linear determinants, page 7106, left column, first sentence of the section relating to ELISA.

Because Nakano et al. relate to antibodies that bind to linear epitopes and the instant invention relates to antibodies that bind to conformational epitopes, Nakano et al. cannot and do not anticipate the instant invention.

Thus, the rejection must be removed.

b) Claims 4 and 17 were rejected over Persson & Allander. Persson & Allander is alleged to teach the use of a phage display library for expressing antibody fragments.

Hepatitis C Virus (HCV) shows a strong genotypic variability (e.g., the genotypic variability of glycoprotein E2 is < 70%) and additionally a subtype-variance (e.g., the homology between different subtypes of viral glycoprotein is < 80% based on the amino acid sequence).

This variability is reflected by the various monoclonal and polyclonal antibodies generated by the prior art. Since the prior art aimed at providing tools recognizing specific epitopes, the resulting antibodies of the prior art are entirely different from the antibodies of this invention.

Persson & Allander disclose recombinant antibodies directed against HCV epitopes of the 2b genotype, and antibodies wherein the variable heavy chains and the variable light chains share a homology of $\geq$ 60%.

In contrast thereto, the antibodies of the present application share sequence homology to the disclosed sequences of Persson & Allander of less than or equal to 54%.

Thus, the person skilled in the art would conclude from such data that the antigenic epitopes bound by said antibodies cannot be identical.

Accordingly, anticipation does not exist and the rejection cannot stand.

c) In Item 17 on page 8 of the Office Action claim 4 was rejected under 35 U.S.C. §102(b) over Cardoso et al.

The data of Cardoso et al. demonstrate an inconsistency which questions the specificity and properties of the Cardoso et al. antibodies, see, for example, Table 1

thereof. Moreover, the function of the Cardoso et al. antibodies is not disclosed, for example, there is no mention of neutralization of binding activity, and there is no evidence that property is inherent in any of the Cardoso et al. antibodies.

As noted on page 7, first full paragraph of the instant application, the antibodies of interest bind to different genotypes, unlike those of Cardoso et al. Thus, while the Cardoso et al. antibodies bind genotypes 1a and 1b only, an instant antibody also binds to those genotypes and to genotypes 2a, 3a and 4.

Thus, anticipation does not lie and the rejection must be removed.

d) At the bottom of page 8 of the Office Action, claim 17 was rejected under 35 U.S.C. §102(b) over Burioni et al.

Burioni et al. was published in September 1988, subsequent to the PCT filing date of the instant 371 national stage application thereof. Hence Burioni et al. is not an effective reference as to the instant invention and application and the rejection must be withdrawn.

e) In Item 22 on page 9 of the Office Action, claim 4 was rejected under 35 U.S.C.§102(b) over Deleersnyder et al.

The monoclonal antibody disclosed in Deleersnyder et al. is directed against the E1/E2 complex of HCV of the 1a genotype. The antibody of the instant application, in contrast, recognizes an epitope located on E2.

Thus, the epitopes are not identical, the antibodies cannot be the same, anticipation does not exist and the rejection must be withdrawn.

f) In Item number 24 on page 9 of the Office Action, claim 4 was rejected under 35 U.S.C.§102(b) over Rosa et al.

From the teaching in the left column on page 1760, first full paragraph, of Rosa et al., the antigens were sometimes fragments of E2 and thus likely led to antibodies that detect linear epitopes.

Rosa et al. disclose polyclonal sera directed against the HCV E2 glycoprotein of the HCV 2 and 3a genotypes and a monoclonal antibody directed against the hypervariable region of E2 of the 1a genotype of HCV. Said hypervariable region is located in front of the epitope bearing region of an antibody of the instant application. Therefore, the specificity of said antibodies is different.

Some of the exemplified antibodies of the instant application were obtained from two patients infected by an HCV-strain of the genotype 4 or 1b. The claimed antibodies cross-react with E2 antigens derived from the genotype 1a of HCV suggesting that the determinant(s) targeted by the claimed antibodies are conserved among at least two of the main prevalent viral subtypes found in the world (subtypes 1(a) and 1(b)). An advantageous result obtained in accordance with the present invention was the demonstration that the antibodies display strong NOB activity, indicating that the determinant(s) recognized by such NOB antibodies are likely directed at conformation-dependent domains of E2. Therefore, these domains are conserved among different genotypes.

Hence, Rosa et al. do not teach the claimed invention and thus, the rejection can be removed.

VII. At the top of page 10 of the Office Action, claims 1 – 4 and 17 were rejected under 35 U.S.C. § 103(e) over Cardoso et al. and Perrson et al.

The rejection is traversed for the following reasons.

The comments with respect to the two references provided hereinabove, are incorporated herein by reference.

As mentioned, Cardoso et al. neither teach, explicitly or inherently, nor suggest the claimed invention. According to the Examiner, Persson & Allander teach an assay. However, neither reference suggests or would motivate an artisan to make an antibody of interest.

Thus, a prima facie case of obviousness have not been made.

Moreover, the antibodies of interest react with a range of genotypes and not just to 1a and 1b as do the Cardoso et al. antibodies. The instant antibodies have the unexpected advantage of wide and robust applicability to a range of HCV. Also, the antibodies of interest inhibit binding of HCV to susceptible target cells.

Accordingly, the rejection must be removed.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance. Reexamination, reconsideration, withdrawal of the objections and rejections, and early indication of allowance are requested respectfully. If any questions remain, the Examiner Is urged to contact the undersigned at the local exchange noted below. If any fees are found to be applicable, please charge any additional fees or make any credits to Deposit Account No. 07-1896.

Respectfully submitted,

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